Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations: An Overview

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Background

- Robust safety database is important for adequate risk/benefit assessment
- Collection of data that are not useful may have negative consequences
  - Disincentive to investigator participation in clinical trials
  - May deter conduct of large, simple trials to obtain outcome data, data on long-term drug effects, and comparative effectiveness & safety data
- In late stages of development or postmarketing, collection of all safety data ways not be useful or necessary, and selective, targeted safety data collection may be warranted

Background

- Selective safety data collection may
  - Improve quality and utility of safety database & assessment w/o compromising integrity & validity of trial results and w/o loss of important information
  - Ease investigator burden
  - Lower costs, thereby encouraging conduct of large, simple trials

Background

- FDA has experience with selective data collection, but on informal, case-by-case basis
- Experience has primarily been with large outcome trials
- Guidance goal is to advise on how & when to simplify data collection to keep balance between eliminating excessive data collection & collecting sufficient data to characterize drug's safety profile
- Sponsors considering simplified data collection should consult with FDA review division prior to implementation

When selective data collection is appropriate

- Selective safety data collection is appropriate when the following criteria are met:
  - Number of subjects exposed in previous studies is sufficient to characterize drug's safety profile
  - Occurrence of AEs has been similar across multiple studies
  - Reasonable to conclude that occurrence of AEs in population to be studied will be similar to what was previously observed

When (continued)

- These criteria are most likely to be met for:
  - Postmarketing studies
    - New indications
    - PMRs that focus on particular safety concern(s)
    - Large outcome trials (may sometimes be conducted premarketing) in the same/similar population
  - Late phase 3 trials when a large safety database already exists

What data may be appropriate for selective collection

- Safety data appropriate for reduced or non collection
  - Nonserious AEs (not associated with drug dc)
  - Routine lab monitoring
    - May also be able to reduce frequency of needed monitoring
  - Information on concomitant medications
    - If pharmacalogically unrelated, provided DDIs & metabolic pathways are characterized fully
    - Particularly short-term medications
    - Dose/frequency information not useful
  - History and physical exams

How to selectively collect safety data (possible approaches)

- Prospective identification of data that need not be collected (in study protocol)
- Collection of certain data (more extensive) only in population subset
  - Important to ensure representation from demographic subgroups & renally impaired in the subset
- Decreased frequency of data collection

When not to be selective

- Development programs in which comprehensive data collection is needed
  - Original applications
  - New indication for a marketed drug where there are important differences in patient population, dose, or other conditions of use
  - Orphan indications
  - Where risk may relate to baseline characteristics, larger sample sizes may be needed to characterize

What not to omit

- Safety data that should generally always be collected
  - All safety data for special populations, e.g. children, pregnant women, where data are generally limited
  - Certain AEs (e.g., serious AEs, deaths, events leading to drug discontinuation/dose changes, potentially serious AEs (e.g., suicidality)
  - Data related to study withdrawals
  - Targeted AEs
  - Long-term exposure to chronic treatments to characterize time course of risk

Bottom line

Guidance does not provide new requirements and does not describe data that must not be collected.

It is permissive: describes some types of data that may not need to be collected because they are not useful.

Division of Cardiovascular and Renal Products perspective

- Often enroll >10,000 subjects (mega trials), followed for years
  - RE-LY (dabigatran) enrolled >18,000 patients
  - PLATO (ticagrelor) enrolled >18,000 patients
- Often involve drugs in a class that have previously been studied/approved
  - Angiotensin receptor blockers
  - Platelet inhibitors
  - GPIIb/IIIa inhibitors
- Often been extensively studied
  - Seeking a new indication
  - Risks well characterized.

- If safety profile adequately characterized with smaller group, why collect extensive data on 15,000+ patients?
  - Common adverse reactions can be detected in <1000 patients
  - Most adverse reactions occur soon (months) after starting therapy
  - ICH standards
    - Total database of at least 1500
    - 100 patients followed for at least 1 year

- Development program/Experience with drug class can often direct efficient safety data collection
  - Safety signals can be well studied in earlier phase 3 investigations
    - Liver enzyme testing
  - Known “on target” effects
    - Bleeding with anticoagulants
  - Identify vulnerable populations

Common DCRP Phase 3 protocol Advice

- Large simple trial
- Infrequent visits
- Abbreviated case report forms
- No adjudication of adverse events
- Focus on characterizing adverse events that could represent a new or important risk
  - Collect only AEs that lead to d/c or death
  - Collect only concomitant meds that have salient pharmacodynamic or pharmacokinetic effects
  - Consider closer monitoring a “sample” of sites

Phase IV Safety Studies

- Post marketing requirements (PMRs) to study a safety signal
  - Observational/Claims-based studies
  - Meta-analysis
  - Large clinical trial
- Protocol development
  - Keep in mind safety question and direct data to it (e.g., major cardiovascular events)
  - Choose endpoints with care

Guidance Document: Extent of Safety Data Collection Oncology Trials Perspective

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Decreased Data Collection

Appropriate circumstances:

- Sufficient number of patients studied
- Similar AEs across multiple studies
- AEs will be similar to what was previously studied

Decreased Data Collection

When Comprehensive Data Collection is generally needed

- Original applications
- Differences expected in populations, dose and other conditions of use
- Orphan indications
- Certain adverse event data

Oncology trials perspective

Patient numbers:

- Single trials with small sample size usually basis of approval
  - Typically 300 to 600 per trial

- Larger adjuvant trials provide info with least noise from the disease
  - Adjuvant trials generally completed later in drug development

Oncology trials perspective

Noise in identifying AEs

- Single arm trials
- Active controls
- Add-on trial designs
- Disease characteristics, co-morbidities from prior therapies or other conditions similar to adverse reactions

Oncology trials perspective

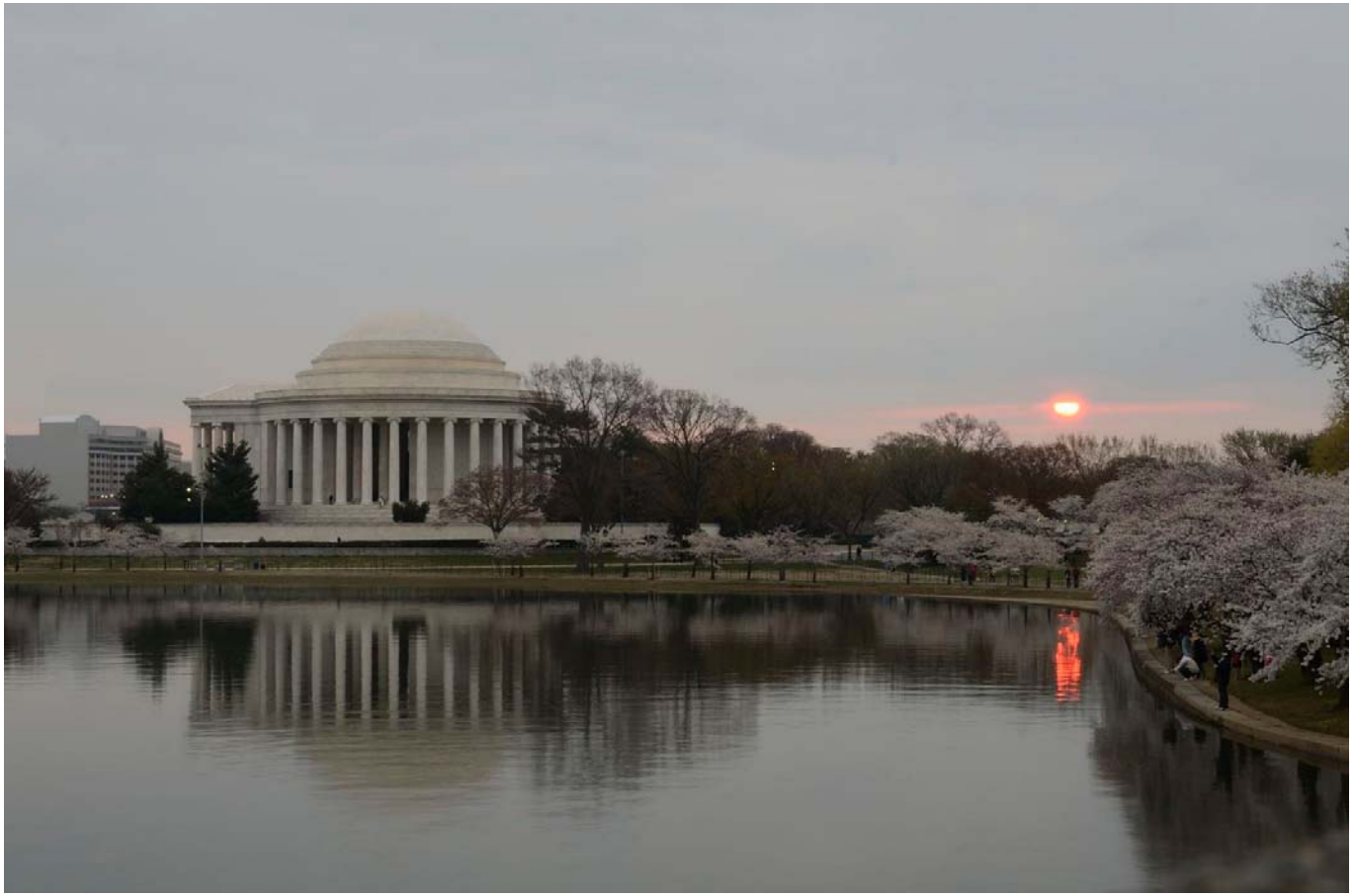
Expectation of similarity in AEs across different studies

- Regimens
  - Different schedules- e.g. weekly vs. 3-weekly
  - Different combinations- e.g. Tykerb with capecitabine or letrozole
  - Impact of prior therapies– e.g. anthracyclines
  - Impact of concurrent therapies- e.g. trastuzumab
- Supplemental applications in different disease types
- Newer therapeutic classes may have AEs different from those of traditional chemotherapy

Examples

- Votrient
  for Renal Cancer:
  - Placebo-controlled trials, N=435 with 2:1 randomization

  for Sarcoma
  - Placebo-controlled trial, N=369 with 2:1 randomization
  - New safety signals: myocardial dysfunction, and pneumothorax
- Hormonal agents for breast cancer



Thank you